UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/002,413	01/02/1998	RICHARD C. ALLEN	311772000500	7792

25226 7590 04/28/2004

MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/002,413	ALLEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42,44-46,48-50,56,57,62,63,65,66 and 68-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,42,44-46,48-50,56,57,62,63,65,66 and 68-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-18-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-1-04 has been entered.

Applicant's arguments filed 6-13-03, paper number 39, have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 55 was canceled on 9-30-02.

Claims 41, 42, 44-46, 48-50, 56, 57, 62, 63, 65, 66 and 68-73 remain pending and under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Claim Rejections - 35 USC 112

Written description

The rejection of claims 56, 57, 62, 63, 66 and 70-73 under 35 U.S.C. 112, first paragraph, has been withdrawn as follows:

The rejection of the phrase "wherein said RPE cells are allogeneic to the mammal" (claim 66) has been withdrawn because claim 12 as originally filed encompassed administering RPE cells "by allograft" as in claim 1.

The rejection regarding the deletion of "allogeneic" in describing the non-RPE in claim 56, 62 and 72 has been withdrawn in view of applicants' arguments.

Enablement

Claims 41, 42, 44-46, 48-50, 56, 57, 62, 63, 65, 66 and 68-73 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal, does not reasonably provide enablement for administering RPE and non-RPE as claimed to increase survival of the non-RPE in the mammal as broadly claimed or to use RPE and non-RPE, specifically RPE and insulin producing β-cells as claimed, to treat a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 41, 42, 44-46, 48-50, 64-66 and 69 are directed toward a method of facilitating survival of an allogeneic graft of non-RPE cells in a mammal by administering retinal pigment epithelial (RPE) cells and non-RPE cells to the mammal, wherein the non-RPE cells are allogeneic to the mammal, and wherein the RPE cells secrete FasL and create localized immunosuppression at the site thereby increasing the survival time

of the allogeneic non-RPE cells. Claims 56, 57, 70 and 71 are directed toward a pharmaceutical composition comprising RPE and insulin-producing β cells. Claims 62 and 63 are directed toward a kit comprising RPE and insulin-producing β cells. Claims 72 and 73 are directed toward an article of manufacture comprising RPE and insulin-producing β cells.

The only disclosed purpose for administering RPE and non-RPE that are allogeneic to the mammal is to treat disease by obtaining therapeutic levels of a biological molecule secreted by the allogeneic cells (pg 4, line 20). The only disclosed purpose for products comprising RPE and insulin-producing β cells (claims 56, 57, 62, 63 and 70-73) is for treating disease.

The state of the art at the time of filing was that symptoms of Parkinson's disease were treated using RPE cells supported by a matrix transplanted into the brain of rats (Cherksey, see the claims, especially claim 13; see also col 17, line 27; col 18, lines 25-44 and col 19, line 24). Cherksey did not explicitly teach co-administering RPE and non-RPE cells, wherein the non-RPE were allogeneic to the host. However, Cherksey suggests transplanting a matrix having both RPE and allogeneic glial cells (col 9, line 2; col 11, line 37).

In addition, the art at the time of filing taught administering non-RPE into mammals to produce therapeutic molecules (Sigalla of record, Sept. 1, 1997, Human Gene Therapy, Vol. 8, pages 1625-1634; pg 1626, col 2, 2nd and 3rd ¶; pg 1628, col 1, 4th ¶ and col 2, 4th and 5th full ¶; Weber of record, 1997, J. Surg. Res., Vol. 69, pg 23-32;

pg 25, col 1, "Islet transplantation"; pg 27, ¶ bridging col 1-2; Fraser of record, 1995, Cell Transplantation, Vol. 4, pg 529-534).

Selawry (1993, Cell Trans., Vol. 2, pg 123) and Selawry (US Patent 5,725,854) taught administering Sertoli cells and pancreatic islet cells such that the sertoli cells create an immune-privileged site and the islet cells produce therapeutic levels of a biological molecule.

While RPE were known to provide "immune privilege" (Ye of record, 1993, Current Eye research, Vol. 12, pg 629-639; pg 629, col. 1, line 1; pg 630, col. 2, line 24; last line of abstract and pg 631, col. 2, line 20), the art at the time of filing did not teach the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal, define the immune response to such a site or teach how to increase survival of allogeneic non-RPE in a mammal using RPE. Therefore, it was unpredictable at the time of filing how to increase survival of allogeneic non-RPE in a mammal using RPE as claimed. Nor did the art at the time of filing teach how to obtain therapeutic levels of biological molecules produced by non-RPE protected within an immune privileged site created by RPE. Therefore, it was also unpredictable at the time of filing how to obtain therapeutic secretion of biological molecules produced by non-RPE protected within RPE cells.

The specification demonstrates isolating and culturing fetal RPE *in vitro* (pg 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pg 21-27). The specification suggests treating a number of diseases (pg 1, line 23; pg 3, line 26; pg 5, line 31), delivering RPE to any of a number of tissues (pg

15, line 7), administering RPE and non-RPE as a single composition or as separate compositions (pg 4, line 23) and using non-RPE such as neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecule (sentence bridging pg 6-7). The specification does not teach administering RPE and non-RPE to a mammal, obtaining a therapeutic effect by administering RPE and allogeneic non-RPE or increasing the survival time of allogeneic non-RPE using RPE.

The specification does not enable administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal such that survival of the graft is facilitated or such that a therapeutic effect is obtained as claimed. A mere suggestion to increase the survival of allogeneic cells or to treat disease in a mammal by administering the allogeneic cells in combination with RPE is inadequate to overcome the unpredictability in the art to use the claimed invention to increase the survival of the non-RPE or to treat disease. The specification does not teach the structure obtained upon administering RPE and non-RPE, the immune response to such a site, the level of secretion of molecules produced by the non-RPE, or treating disease using such a method. The specification does not teach the immune response to such a site or rate of survival of the allogeneic non-RPE cells. The specification does not teach administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal. Therefore, the specification does not overcome the unpredictability in the art by teaching how to use RPE and allogeneic non-RPE to increase survival of the non-RPE or to secrete therapeutically effective amounts of a biologically active molecule from non-RPE in such a site.

Specifically, the specification does not provide any guidance on how to use allogeneic pancreatic islet of Langerhans cells (claims 57, 63, 73) or insulin-producing cells (claim 56, 62, 72) in combination with RPE to treat disease. While Selawry taught using Sertoli cells to deliver β-cells secreting insulin, the specification does not provide adequate correlation between Sertoli cells and RPE such that similar results could be obtained. Pg 3, line 23, states Sertoli cells secrete FasL. But the specification does not teach RPE secrete the same amount of FasL, that the structure of the site created by Sertoli cells and RPE is the same, that biological molecules secrete through a structure created by RPE or that the amount of secretion of a therapeutic protein obtained using RPE cells would be equivalent to that observed using Sertoli cells.

Applicants reiterate the art, the rejection and the claims (pg 9-11).

Applicants argue the specification teaches RPE cells secrete substantial amounts of biologically active FasL on pg 16, lines 18-25, and pg 24-28. Applicants argue the specification teaches RPE conditioned medium induced apoptosis in thymocytes on pg 27, lines 15-37. Therefore, applicants conclude the number of RPE cells needed to provide an immune privileged site and increase survival time of the non-RPE cells can be determined (pg 11, 2nd ¶ of response). Applicants' conclusion cannot be made because the logic is incomplete. One of skill would not conclude that RPE cells would create an immune privileged site simply because FasL was produced by RPE cells *in vitro*; at least a showing that the amount of FasL produced in RPE and Sertoli cells was the same *in vitro* would be required (Sertoli cells being known to create an immune privileged site). One of skill would not conclude that RPE cells created an

immune privileged site because RPE conditioned medium induced apoptosis in thymocytes; other components of the immune system would have to be considered. For example, antibodies may not be affected by FasL and would not be subject to apoptosis because they are not cells.

Applicants argue no particular structure is required in the "site" of localized immunosuppression (¶ bridging pg 11-12). Applicants' argument is in error. The immune-privileged sites in the body feature structural barriers (eye, testes and brain, pg 2, lines 4-8, of instant specification). Selawry taught immune-privileged sites of islet β-cells were partitioned into cell clusters by thin connective septa containing small vessels and capillaries as well as a high density of Sertoli-like cells at the interface of the Sertoli cells and β cells (1993, pg 126, "Tissue Morphology"). Jorgensen (1997 of record) taught immune privileged sites were dependent on physical barriers, absence of lymphatic vessels and expression of FasL. Thus, the specification and the art at the time of filing taught structural features were essential to obtain immune privileged sites.

Applicants' discussion of the obviousness rejection over Cherksey on pg 12 of the response is misplaced. The examiner's discussion of Cherksey under obviousness is separate from the discussion of Cherksey under enablement. In the enablement rejection, applicants have not provided any reasoning why Cherksey does not reflect the state of the art or why the Examiner's interpretation of Cherksey is in error. The enablement rejection has been made based on the unpredictability in the art. The unpredictability in the art has been established by what <u>was</u> known about transplanting RPE cells into a host at the time of filing (i.e. transplanting RPE into the brain with

allogeneic glial cells (Cherksey)) and the dearth of information in the specification and the art at the time of filing regarding how transplanting RPE and allogeneic non-RPE into a host would effect survival of the allogeneic non-RPE cells as compared to other methods. The limitation of "increasing survival time of the allogeneic graft of the population of non-RPE" may be interpreted differently in the obviousness rejection and the enablement rejection.

Applicants' discussion of the previous office action on pg 12-13 is of no legal significance. The previous office action was consistent. The specification merely suggested and did not explicitly teach administering RPE and non-RPE to a mammal, wherein the non-RPE were allogeneic to the mammal. If applicants explicitly taught administering RPE and non-RPE to a mammal, wherein the non-RPE were allogeneic to the mammal, please point to the citation by page and line number. The specification was enabled for administering RPE and non-RPE to a mammal, wherein the non-RPE were allogeneic to the mammal because Cherksey taught administering RPE and non-RPE to a mammal, wherein the non-RPE were allogeneic to the mammal. The therapeutic embodiments and increasing survival of non-RPE cells were not enabled.

Indefiniteness

Claims 41, 42, 44-46, 48-50, 65, 66, 68 and 69 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection of claim 65 regarding the preamble and the body of the claim has been withdrawn. The preamble "facilitating survival of an allogeneic graft of a population of non-RPE cells" has the same scope as "increasing survival time of the allogeneic graft of the population of non-RPE cells." "Increasing" is within the realm of "facilitating" and "survival time" is within the realm of "survival." The language could be further clarified. I.e. use "increasing survival of non-RPE cells" in the preamble and "increasing survival of the non-RPE cells" in the body of the claim. Claim 65 already requires that the non-RPE cells are allogeneic to the RPE cells; therefore, reference to "an allogeneic graft of a population of" is extraneous. This is an objection to claim 65, not a rejection.

Claim 65 remains indefinite because it is unclear to what the survival time of the population of non-RPE cells is being compared. Is the survival time greater in the mammal than *in vitro*? Greater in the mammal using RPE as compared to administering the non-RPE cells alone? Greater than administering autologous non-RPE? As such the metes and bounds of when increased survival time of the non-RPE has been obtained cannot be determined. Overall, the result of administering RPE and non-RPE still cannot be determined. Applicants again quote pg 4 and 7 and conclude "these statements make clear that the RPE cells increase survival of the co-administered non-RPE in the mammal, as opposed to survival of the non-RPE cells administered alone or survival of the non-RPE cells *in vitro.* None of the citations discuss what to being compared to the survival time of non-RPE cells with RPE cells. One of skill certainly would never have guessed that citations on pg 4 and 7 meant the

non-RPE cells in the method had increased survival as compared to "non-RPE cells *in vitro*" as in applicants' arguments.

Claim Rejections - 35 USC 103

Claims 41, 42, 44-46, 48, 49, 65 and 68-71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record as supported by Jorgensen (1997, Invest. Ophthalmology and Visual Sci., Vol. 38, No. 4, part 1-2, pg 2186, Abstract 924).

Cherksey taught treating symptoms of Parkinson disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also col. 17, line 27; col. 18, lines 25-44 and col. 19, line 24). RPE cells inherently secrete FasL and create localized immunosuppression (pg 2, line 27, of the specification). Cherksey did not explicitly teach co-administering RPE and non-RPE cells.

However, Cherksey suggests transplanting a matrix having both RPE and glial cells attached (col. 9, line 2) and that the glial cells may be allogeneic to the host (col. 11, line 37).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic to the host as taught by Cherksey. One of ordinary skill in the art at the time the invention was made would have been motivated to add glial cells to the RPE as suggested by Cherksey and to treat neural disorders in the brain. Motivation to use

RPE cells as the cells injected into the brain is provided by Jorgensen who taught RPE cells secreted FasL, a protein known to be associated with the ability to create an immune privileged site (see entire abstract).

The method of Cherksey increases "survival time" of the glial cells as compared to leaving the glial cells on the counter. The method of Cherksey increases "survival time" of the glial cells as compared to administering allogeneic glial cells without RPE because RPE inherently secrete FasL causing an "immune privilege site." Case law established that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Jorgensen provides support that the one of ordinary skill would reasonable expect to create localized immunosuppression using the method of Cherksey because Jorgensen taught RPE cells induced apoptosis of activated T cells, Jurkat T cells and primed T cells and secreted FasL ligand.

Applicants summarize the invention and the claim in the paragraph bridging pg 16-17 of the response. Applicants summarize the teachings of Cherksey in the first line of the first full paragraph on pg 17. Applicants' summary of the invention, the claims and Cherksey are adequate. However, applicants' summary of the deficiencies of Cherksey (second sentence of 1st full ¶ on pg 17) is in error. Applicants state Cherksey does not teach or suggest the use of neural or paraneural cells create an immune privileged site, much less the use of RPE cells to create local immunosuppression. First the claims in the instant application are limited to RPE, not neural or paraneural cells. Second, Cherksey taught administering RPE with allogeneic glial cells into a patient.

Third, the method taught by Cherksey inherently results in secretion of FasL (see the instant specification on pg 2, line 27, and Jorgensen of record), thereby inherently creating "localized immunosuppression" as claimed. Therefore, Cherksey need not teach that which is inherent upon transplanting RPE and glial cells into a host. Case law established that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Applicants' statement that "there is no motivation, in Cherksey or in the art, to modify the teachings of Cherksey to arrive at the claimed invention" (pg 17 of response, last sentence of 1st full ¶) is unfounded. No reasoning or error has been provided.

Applicants argue that without recognition that RPE cells secrete FasL to create local immunosuppression there is no motivation for one to modify the teaching of Cherksey and specifically select RPE cells from the various neural and paraneural cells taught in Cherksey for use in the presently claimed invention." Applicants' argument is in error. First, Cherksey specifically pointed to RPE cells throughout the specification and obtained claims to a method for increasing the viability of RPE injected into the mammalian brain by adhering RPE to the surface of a support matrix and injecting the adhered cells into a mammalian brain, whereby the injected cells remain viable for at least two months (6, 13 and 16). Therefore, the requirement for one of ordinary skill to select RPE is unfounded because Cherksey specifically suggested using RPE. Second, the desire to create local immunosuppression is not required because it occurs inherently. Third, Jorgensen provides motivation to select RPE because they induce

apoptosis in T cells and secrete FasL. Fourth, the brain already has "localized immunosuppression" because it is an immune privileged site. Therefore, Cherksey teaches all the steps required to obtain FasL secretion and local immunosuppression.

Applicants argue Cherksey did not specifically state the glial cells in col. 9, line 2, would be allogeneic. Applicants argue Cherksey did not specifically state the glial cells may be allogeneic in col. 11, line 37 (pg 19 of response, 1st ¶). Applicants' arguments are not persuasive. One of ordinary skill in the art at the time the invention was made would have reasonably determined that "[t]he cells useful in the method" that "may be... ...allogeneic" described in col. 11, line 37, applied to any of the cells described in the application, including the glial cells in col. 9, line 2.

Applicants argue Cherksey did not provide a reasonable expectation of success for the claimed invention because Cherksey did not suggest using RPE to create an immune privileged site (pg 19 of response, 2nd ¶). Applicants' logic is flawed. The brain is already an immune privileged site, so Cherksey provides a reasonable expectation of protecting the RPE and glial cells from the immune system because they are in the brain. Furthermore, one of ordinary skill in the art would have a reasonable expectation of success in using RPE cells to create an immune privileged site because Jorgensen taught RPE cells expressed FasL and induced apoptosis in T-cells.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER